PART VI: Summary of the risk management plan by product

Active substance	*Mercaptamine hydrochloride*
Product(s) concerned (brand name(s)):	CYSTADROPS ®
MAH/Applicant name	Recordati AG

Data lock point for this module:	31 October 2020
Version number of RMP when this module was last updated	: Version number: 2.0
QPPV name:	Kehal Kawthar
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The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them.

The RMP summary of "Cystadrops" is a concise document and does not claim to be exhaustive.
As the RMP is an international document, the summary might differ from the "Arzneimittelinformation / Information sur le médicament" approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization.

Please note that the reference document which is valid and relevant for the effective and safe use of "Cystadrops" in Switzerland is the "Arzneimittelinformation / Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic. "Recordati AG" is fully responsible for the accuracy and correctness of the content of the published summary RMP of "Cystadrops"

VI.1 Elements for summary tables in the EPAR

VI.1.1 *Summary table of Safety concerns*

Important identified risks	• Severe eye irritation
Important potential risks	• Punctate keratopathy and/or toxic ulcerative keratopathy (due to BAK) • Corneal neovascularisation • Ocular manifestations of EDLS • Increased risk of infection and medication error due to device assembly failure
Missing information	• Patients with other ocular co-morbidities • Patients receiving concomitant treatment with ophthalmic products containing BAK • Long-term safety

BAK=Benzalkonium chloride; EDLS=Ehlers-Danlos like syndrome.

VI.1.2 *Table of on-going and planned studies in the Post-authorisation Pharmacovigilance Development Plan*

Study title Status	**Summary of objectives**	**Safety concerns addressed**	**Status**	**Date for submission of interim or final reports (planned or actual)**
Category 3 - Required additional pharmacovigilance activities				
Open-label, longitudinal, Post-Authorisation Safety Study to assess the safety of Cystadrops® in paediatric and adult cystinosis patients in long-term use. Ongoing	To assess and characterise the long-term safety of Cystadrops in pediatric and adult patients with cystinosis, who were followed-up for 5 years.	• Severe eye irritation • Punctate keratopathy and /or toxic ulcerative keratopathy (due to BAK) • Corneal neovascularisation • Ocular manifestation of EDLS • Increased risk of infection and medication error due to device assembly failure • Long-term safety	• Ethics submission. • Start of data collection. • • End of data collection. • • Study Progress Report. • Final Report of study results.	• Fourth quarter of 2018. • First quarter of 2019. • First quarter of 2025. • Annually throughout the study and in line with the Periodic Safety Update Reports for Cystadrops. • Approximately ≤1 year after database lock.

VI.1.3 Summary of Post authorisation efficacy development plan

No post-authorisation Risk Minimisation Measures efficacy studies are planned for Cystadrops.

VI.1.4 *Summary table of Risk Minimisation Measures*

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risks		
Severe eye irritation	Routine risk minimisation measures: Section 4.4 of the SmPC which notes that Cystadrops contains BAK which may cause eye irritation. Section 2 of the PL which notes that BAK may cause eye irritation and Section 3 where it is advised that patients remove excess medicine around the eye to avoid potential irritation. Section 4.8. of the SmPC and Section 4 of the PL where Eye irritation is listed as an undesirable/side effect for Cystadrops. Legal status: Subject to restricted medical prescription. Treatment should be supervised by a physician experienced in the management of cystinosis. Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: PASS CYT-DS-001
Important potential risks		
Punctate keratopathy and/or toxic ulcerative keratopathy (due to BAK)	Routine risk minimisation measures: Section 4.4 of the SmPC which notes that BAK, which is commonly used as a preservative in ophthalmic products, has also been reported to cause punctate keratopathy and/or toxic ulcerative keratopathy. Legal status: Subject to restricted medical prescription. Treatment should be supervised by a physician experienced in the management of cystinosis. Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: PASS CYT-DS-001
Corneal neovascularisation	Routine risk minimisation measures: Legal status: Subject to restricted medical prescription. Treatment should be supervised by a physician experienced in the management of cystinosis. Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: PASS CYT-DS-001
Ocular manifestations of EDLS	Routine risk minimisation measures: Section 4.8 of the SmPC which lists Ocular hyperaemia as an undesirable effect for Cystadrops.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Legal status: Subject to restricted medical prescription. Treatment should be supervised by a physician experienced in the management of cystinosis. Additional risk minimisation measures: None.	Additional pharmacovigilance activities: PASS CYT-DS-001
Increased risk of infection and medication error due to device assembly	Routine risk minimisation measures: Section 6.6 of the SmPC and Section 3 of the PL where it is advised that patients wash their hands carefully in order to avoid microbiological contamination of the content in the vial. Section 3 of the PL which includes a QR code linked to a video advising how to use Cystadrops. Legal status: Subject to restricted medical prescription. Treatment should be supervised by a physician experienced in the management of cystinosis. Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: PASS CYT-DS-001
Missing information		
Patients with other ocular co-morbidities	Routine risk minimisation measures: Legal status: Subject to restricted medical prescription. Treatment should be supervised by a physician experienced in the management of cystinosis. Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.
Patients receiving concomitant treatment with ophthalmic products containing BAK	Routine risk minimisation measures: Section 4.4 of the SmPC which notes that BAK, which is commonly used as a preservative in ophthalmic products, has also been reported to cause punctate keratopathy and/or toxic ulcerative keratopathy; therefore, monitoring is required. Legal status: Subject to restricted medical prescription. Treatment should be supervised by a physician experienced in the management of cystinosis. Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Long-term safety	Routine risk minimisation measures: Legal status: Subject to restricted medical prescription. Treatment should be supervised by a physician experienced in the management of cystinosis. Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: PASS CYT-DS-001

PASS=post-authorisation safety study; PL=Package Leaflet; SmPC=Summary of Product Characteristics.

VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Corneal cystine crystal deposits in adults and children from 2 years of age with cystinosis

Cystinosis is an ultra-rare (ultra-orphan) disease, with low incidence and prevalence rates globally. Epidemiological studies of cystinosis are sparse, and recent data on the prevalence and incidence of the disease are limited. Higher incidence rates of cystinosis have been reported in selected populations around the world as a result of the extent of consanguinity within specific communities. Data specifically reporting on the incidence of nephropathic cystinosis, as opposed to cystinosis more generally, is particularly uncommon. The estimated worldwide incidence of nephropathic cystinosis is 1 in 100 000 to 200 000 live births. Since the introduction of cysteamine therapy, the life expectancy of nephropathic cystinosis patients in developed countries has extended beyond 50 years. The prevalence of cystinosis is extremely low, affecting only an estimated 2000 individuals worldwide.

VI.2.2 Summary of treatment benefits

The clinical development programme for Cystadrops included 2 RRD-sponsored clinical trials; a Phase III study (Cysteamine hydrochloride for nephropathic cystinosis [CHOC]) and a Phase I-IIa study (Adaptive dose regimen of Cystadrops for corneal crystal deposits [OCT-1]), with a total of 40 subjects enrolled.

CHOC study: this study was an open-label, randomised, comparative trial lasting for 3 months at a dose regimen of 4 drops/eye/day. The primary objective of this study was to compare the efficacy of Cystadrops versus CH 0.10% eye solutions. Superiority of Cystadrops efficacy was demonstrated compared to the control arm (cysteamine hydrochloride. Superiority of Cystadrops was also demonstrated for photophobia rated by the investigator compared to the control arm (cysteamine hydrochloride 0.10%).

OCT-1 study: this study was an open-label, single-group trial with an extended follow-up period of 5 years. In the OCT-1 study, treatment with Cystadrops led to a significant reduction in the mean In-Vivo Confocal Microscopy (IVCM) total score with respect to baseline, which remained relatively constant, for up to 60

months. Furthermore, a lower Corneal cystine crystal score (CCCS) and reduced crystal thickness confirmed the reduction in corneal cystine crystal deposits. With treatment, an improvement in photophobia was also noted.

VI.2.3 Unknowns relating to treatment benefits

There are limited or no information concerning Cystadrops in pregnant and breastfeeding women, and in patients with other ocular comorbidities and patient receiving concomitant treatment with ophthalmic products containing BAK. Therefore, it is unknown whether use of Cystadrops in these populations will be profitable and safe.

VI.2.4 *Summary of safety concerns*

Important identified risks

Risk	What is known
1. Severe eye irritation	Section 4.4 of the SmPC for Cystadrops states that 'Cystadrops contains benzalkonium chloride which may cause eye irritation'. Section 4.8 of SmPC for Cystadrops also notes that Eye irritation is among the most common adverse reactions for Cystadrops. Cumulatively, a total of 213 adverse events (AEs; all non-serious) pertaining to severe eye irritation have been identified from the NPU programmes, post-marketing data, clinical trials and a non-Orphan Europe-sponsored study. Therefore, it is considered that there is sufficient evidence to classify severe eye irritation as an important identified risk for Cystadrops.

AE=adverse event; NPU=Named Patient Use; SmPC=Summary of Product Characteristics.
Source: NPU programmes, post-marketing data, clinical trials, a non-Orphan Europe-sponsored study and the SmPC for Cystadrops.

Important potential risks

Risk	What is known
1. Punctate keratopathy and/or toxic ulcerative keratopathy (due to BAK)	Section 4.4 of the SmPC for Cystadrops states that 'Benzalkonium chloride, which is commonly used as a preservative in ophthalmic products, has also been reported to cause punctate keratopathy and/or toxic ulcerative keratopathy. Monitoring is required'. Cumulatively, a total of 9 events (all serious) pertaining to punctate keratopathy and/or toxic ulcerative keratopathy (due to BAK) have been identified from the French ATU programme and a non-Orphan Europe-sponsored study. Therefore, punctate keratopathy and/or toxic ulcerative keratopathy (due to BAK) is considered as an important potential risk for Cystadrops.
2. Corneal neovascularisation	In general, corneal neovascularisation can lead to a profound decline in vision. The abnormal vessels block light, cause corneal scarring, compromises visual acuity, and possibly leads to inflammation and oedema. Cumulatively, 1 serious event pertaining to corneal neovascularisation has been identified from clinical trials. Therefore, corneal neovascularisation is considered as an important potential risk for Cystadrops.
3. Ocular manifestations of Ehlers-Danlos like syndrome (EDLS)	Tsilou et al (2002) discussed the age-related prevalence of anterior segment complications in cystinosis patients. Of 10 renal transplant recipients, a 19-year-old patient with nephropathic cystinosis had pupillary block glaucoma that was attributed to iris thickening and decreased motility. In 172 cystinosis patients, a 38-year-old woman and 29-year-old man developed a phthisical eye due to posterior synechiae and angle-closure glaucoma [Tsilou et al, 2002]. In both eyes of a 33-year-old dead patient, donated for pathology, microscopic examination disclosed retinal detachment [Tsilou et al, 2007]. Cumulatively, no other events pertaining to ocular manifestations of EDLS have been identified from NPU programmes and clinical trials. Section 4.8 of the SmPC for Cystadrops states that ocular hyperaemia is among the most common adverse reactions in patients using Cystadrops. Also, ocular manifestations of EDLS can lead to visual impairment. Therefore, ocular manifestations of EDLS is considered as an important potential risk for Cystadrops.
4. Increased risk of infection and medication error due to device assembly failure	Ocular infection can lead to various degrees of visual impairment and, in the worst case, to vision loss. Medication error due to device assembly failure can lead to corneal cystine crystal deposits accumulation and worsening of ocular cystinosis symptoms. Cumulatively, a total of 22 AEs (all non-serious) pertaining to Increased risk of infection and medication error due to device assembly failure have been identified from NPU programmes, post-marketing data and clinical trials. Therefore, increased risk of infection and medication error due to device assembly failure is considered as an important potential risk for Cystadrops.

Missing information

Risk	What is known
1. Patients with other ocular co-morbidities	There is limited information on the use of Cystadrops in patients with other ocular co-morbidities. Therefore, the anticipated risk of the use of Cystadrops in patients with other ocular co-morbidities remains to be further investigated and is considered missing information.

Risk	What is known
2. Patients receiving concomitant treatment with ophthalmic products containing BAK	Section 4.4 of the SmPC for Cystadrops states that 'Benzalkonium chloride, which is commonly used as a preservative in ophthalmic products, has also been reported to cause punctate keratopathy and/or toxic ulcerative keratopathy. Monitoring is required'. There is limited information on the use of Cystadrops in patients receiving concomitant treatment with ophthalmic products containing BAK. Therefore, patients receiving concomitant treatment with ophthalmic products containing BAK is considered as missing information for Cystadrops.
3. Long-term safety	There is limited information on the long-term safety of Cystadrops. Therefore, the anticipated risk of the long-term use of Cystadrops remains to be further investigated and is considered missing information.

VI.2.5 *Summary of risk minimisation measures by safety concern*

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimisation measures.

This medicine has no additional risk minimisation measures (only routine risk minimisation measures).

VI.2.6 *Planned post authorisation development plan*

No post-authorisation Risk Minimisation Measures efficacy studies are planned for Cystadrops.

VI.2.7 Summary of changes to the Risk Management Plan over time

Table 1. Major changes to the Risk Management Plan over time

Version	Approval date	Change
1.3	30 September 2015	Not applicable; this is the first RMP for Cystadrops.
2.0	01 April 2019	• Conversion of RMP to Good Pharmacovigilance Practices Module V Revision 2. • Updates regarding a post-authorisation safety study.